Mitochondria are cellular structures whose main function is the production of energy during cellular respiration in the process of so-called oxidative phosphorylation taking place on the respiratory chain located in the inner mitochondrial membrane. Mitochondria are built of c.a. 1500 different proteins and information about the sequence of the vast majority of them is encoded in the genetic material in the nucleus of the cell, and only 13 proteins are encoded in genetic material in mitochondrion (mtDNA). Detailed analyses carried out in recent years showed, that mtDNA also contains information about a number of short peptides with significant cytoprotective properties. The best described mitochondrial peptide is humanin, which has been shown to improve the mitochondrial function and reduce the production of reactive oxygen species in many cellular models. Mutations in genes encoding mitochondrial proteins lead to the development of mitochondrial diseases, which symptoms mainly affect those tissues that have a high energy demand – like the nervous system and muscles. So far, no effective and safe method of treating this group of genetic disease has been developed.

The proteasome is a protein complex responsible for selective degradation of most proteins in a cell that regulates a number of processes necessary to maintain intracellular balance. Mitochondrial proteins, which synthesis takes place in the cytoplasm have to be actively transported to the mitochondria, and our research group indicated that proteasome plays an important role in the control of proteins transported to the mitochondria, what makes proteasome co-responsible for the proper function of these significant cell organelles. Chemicals with the ability to inhibit the activity of the proteasome, called inhibitors, through the confirmed effectiveness in the activation of cell death in many studies, have found application in oncological therapy. The latest studies of our group indicate, that proteasome inhibition could be an innovative and effective method of treatment of mitochondrial diseases. Analyses on cell line derived from a patient with mitochondrial encephalopathy have shown, that the use of proteasome inhibitors resulted in the inhibition of degradation of the mitochondrial mutant protein and its increased transport from the cytoplasm to the mitochondria and improved respiratory chain activity. Despite the proven efficacy of proteasome inhibitors in cancer therapy, these compounds cause a number of side effects in patients, most notably cardiovascular dysfunctions and neurological disorders, the causes of which are not specified, however the toxic effect of therapy on mitochondrial function is indicated as one of the factors, therefore before proteasome inhibitors will be adapted in the mitochondrial diseases treatment, we need to evaluate the effect of these drugs on the function of mitochondria.

In the presented project we plan to perform three main research tasks. The first two will focus on the analysis of the effects of various proteasome inhibitors on mitochondrial metabolism and mitochondrial protein homeostasis in various human cell models carrying “healthy” mitochondria as well as in cells with mutations in genes encoding mitochondrial proteins, including cell lines derived from patients with mitochondrial diseases. We want to check whether inhibition of the proteasome contributes to dysfunction of the mitochondria. In addition, we will compare changes in mitochondrial metabolism due to proteasome inhibition between lines containing fully functional and defective mitochondria. In the last task we want to assess whether the two mitochondrial-derived peptides – humanin and its more biologically active analog humanin G, will be able to suppress the toxic effects of proteasome inhibitors on the mitochondria.

The results of the planned research will provide new knowledge on the effects of proteasomal inhibition on mitochondrial physiology, and the toxicity of proteasome inhibitors. Interestingly, good candidates to improve mitochondrial function in the cells, in which the proteasome has been inhibited, are mitochondrial-derived peptides. Thus, this knowledge can be a basis for designing appropriate therapy to increase the effectiveness of the treatment of both cancer and mitochondrial diseases while minimizing its side effects.